

# Does Tooth Extraction and Perioperative Medication Affect PT-INR of Patients Taking Warfarin?

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## Research article

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# Abstract

**Background:** Various antibiotics and analgesics have been reported to interact with warfarin. Reports that investigate the effects of medication taken for just a few days during tooth extraction on the prothrombin time-international normalized ratio (PT-INR) are rare.

**Methods:** A total of 110 patients receiving long-term stable warfarin therapy underwent tooth extraction without interruption of warfarin treatment. INR values were measured one month before the tooth extraction, the day of the extraction, and one week after the extraction. We investigated the changes of INR values between the day of extraction and one week after the extraction, as well as the various risk factors for increases in INR values.

**Results:** Before and after tooth extraction, the number of patients taking cefcapene pivoxil, amoxicillin, and azithromycin was 57, 36, and 8, respectively. Nine patients were administered ampicillin before tooth extraction and received amoxicillin after their tooth extraction. One week after tooth extraction, the INR values increased beyond the therapeutic range in 3 out of 110 patients (2.7%). The INR values before tooth extraction in these three patients were close to 3.0. The INR value increased by more than twice as much in 1 of 110 patients (0.9%).

**Conclusion:** When a tooth extraction is performed in patients taking warfarin, certain factors could increase the INR, such as interaction between warfarin and antibiotics or analgesics, post-extraction inflammation or infection, and eating disorders due to post-extraction pain. However, our results suggest that it has little effect on the INR values one week after extraction.

## 1. Background

Various antibiotics and analgesics have been reported to interact with warfarin [1–5]. For tooth extraction, patients are usually prescribed antibiotics in order to prevent surgical site infection (SSI) or Infective endocarditis (IE), and analgesics to decrease pain. These drugs may also interact with warfarin and produce a clinically significant alteration in anticoagulation status. However, most previous reports were on long-term treatment cases and cases where oral intake was not possible [1–5]. To our knowledge, there is only one report that investigated the effects of medication that was administered for just a few days for tooth extraction on the prothrombin time-international normalized ratio (PT-INR) [6]. This study investigated the effect of azithromycin (AZM) on INR values in patients taking warfarin [6].

In the present study, we retrospectively investigated the effects of various antibiotics and analgesics administered during tooth extraction on the INR values in patients who were on stable warfarin therapy.

## 2. Methods

### 2.1. Patients

In this study, inclusion criteria was set for patients above eighteen years old, and exclusion criteria was set for patients who hoped non-participate after the publication of this study. From January 2014 to December 2019, 110 patients taking warfarin underwent tooth extraction at Kakogawa Central City Hospital. Before tooth extraction, all patients consulted their primary physicians regarding their general medical status and the use of anticoagulants. If their INR values were over 3.0, they were advised to postpone the extraction, according to the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction<sup>15</sup> and the Guidelines for Pharmacotherapy of Atrial Fibrillation [7, 8]. In the past, several studies reported that INR values increased beyond the therapeutic range one week after oral administration of antibiotics [9, 10]. Based on these reports, our hospital routinely measures patients' INR values on the day of their tooth extraction when they are taking warfarin and are re-measured again one week after.

## 2.2. Medication

The types (e.g., cefcapene pivoxil [CFPN-PI], amoxicillin [AMPC], AZM), and dosages of antibiotics were chosen at the discretion of the physicians; these were taken one hour before tooth extraction and for a few days after extraction in order to prevent SSI. If the patients had a valvular disease, ampicillin (ABPC) was administered 30 minutes before extraction in order to prevent IE. This was in accordance with the Guidelines for Prevention and Treatment of Infective Endocarditis (Japanese Circulation Society 2008, 2017) [11]. For analgesics, only acetaminophen (APAP) was prescribed for several days.

## 2.3. Surgical procedures

All patients continued taking warfarin and were hospitalized from the day of their tooth extraction to the following day. Tooth extraction was performed under local anesthesia, administered as 1.8–3.6 mL of 2% lidocaine containing 1/80000 units of epinephrine. The teeth were extracted by a rotation and traction movement with forceps or elevators. If immediate hemostasis was not achieved with a dry gauze compression for 5 min, then a hemostat composed of oxidized cellulose (surgical; Ethicon, Somerville, NJ, USA), sutures with 3 - 0 absorbent thread, or a surgical splint was used at the surgeon's discretion. After confirming hemostasis during the tooth extraction, all patients were instructed to bite down on the gauze for a few hours in each hospital room. In all patients, the presence of hemorrhage was checked by surgeons a few hours after the tooth extraction. If the hemorrhage required additional treatment such as re-suturing, we defined it as a post-extraction hemorrhage.

## 2.4. Variables

We investigated the rates of the changes of the INR values beyond the therapeutic range one week after their tooth extraction. Additionally, the following variables from medical records were retrospectively reviewed: (1) medication—types; (2) patient details in terms of—sex, age, warfarin dose, diabetes mellitus, hypertension, cerebral infarction, antiplatelet therapy status (single or dual), preoperative non-steroidal anti-inflammatory drugs (NSAIDs) being taken, serum creatinine levels, estimated glomerular filtration rates (eGFR), and alanine transaminase (ALT) levels; (3) surgical details including the—number of extracted teeth and whether they had a post-extraction hemorrhage.

## 3. Results

### 3.1 All patients

Before and after tooth extraction, the number of patients taking cefcapene pivoxil, amoxicillin, and azithromycin was 57, 36, and 8, respectively. Nine patients received ampicillin before-tooth extraction and received amoxicillin after-tooth extraction.

### 3.2 Patients who took CFPN-PI and APAP

From January 2014 to June 2016, CFPN-PI was the primary antibiotic used to prevent SSI. All 57 patients received 300 mg of CFPN-PI per day for three days before and after tooth extraction, followed by 1200-1800mg of APAP per day for three days after tooth extraction. Seven out of the 57 patients underwent additional treatments due to post-extraction hemorrhages on the day of extraction.

The INR values increased beyond the therapeutic range in 1 out of 57 patients (Fig. 1). We present this patient as Case A. Case A took 300 mg of CFPN-PI per day for three days, followed by 1800 mg per day for three days like the other patients, and had 12 teeth (the greatest number of teeth of the 57 patients) extracted. The patient's INR value was within the therapeutic range, but was the highest out of all 57 patients, with a value of nearly 3.0 one month before tooth extraction and on the day of the extraction (2.93, 2.81) (Fig. 1).

### 3.3 Patients who took AMPC and APAP

From July 2016 to December 2019, AMPC was the main antibiotic prescribed, as opposed to CFPN-PI. Most of the 36 patients took AMPC at a dose of 750 mg/day for two days (two patients took it for three days) before and after tooth extraction, and APAP at a dose of 1200 mg/day for 3–7 days after tooth extraction. One patient underwent additional treatments due to post-extraction hemorrhages on the day of extraction.

### 3.4 Patients who took ABPC, AMPC and APAP

Most of the nine patients were treated with a single 2-g dose of ABPC the day before tooth extraction, and then took AMPC at a dose of 750 mg/day for two days (just one patient took it for four days), and 1200–1500 mg/day of APAP for 3–7 days after tooth extraction. Two out of the nine patients underwent additional treatments due to post-extraction hemorrhages on the day of extraction, and one out of two patients had a post-extraction hemorrhage after discharge.

One week after their tooth extraction, the INR value in one patient increased by more than twice as much (Fig. 1). We present this patient as Case B. Case B had two teeth extracted and was treated with a single 2-g dose of ABPC the day before tooth extraction, and then took AMPC at a dose of 750 mg/day for two days like the other patients. This patient had a post-extraction hemorrhage on the day of the extraction and visited our hospital due to re-post-extraction hemorrhage two days after tooth extraction as well.

After the patient's hemostasis was treated, they were prescribed AMPC for two days and APAP for three days. In addition, the patient's INR value was within the therapeutic range, but had a value close to 3.0 both one month before tooth extraction and on the day of the extraction (2.73, 2.73) (Fig. 1).

### **3.5 Patients who took AZM and APAP**

AZM was mainly used for patients with impaired liver function or a penicillin allergy. All eight patients took AZM at a dose of 500 mg/day for three days before and after tooth extraction, and 1200–1500 mg/day for 3–7 days after tooth extraction. None of the patients had post-extraction hemorrhages.

One week after tooth extraction, a patient's INR value increased beyond the therapeutic range (Fig. 1). We present this patient as Case C. Case C had one tooth extracted and took AZM at a dose of 500 mg/day for three days, followed by 1200 mg/day of APAP for seven days. However, while Case C's INR was within the therapeutic range, it was the highest of all eight patients in this group, with a value close to 3.0 both one month before tooth extraction and on the day of the extraction (2.70, 2.90) (Fig. 1).

## **4. Discussion**

In the present study, we investigated the effects that various antibiotics and analgesics taken during tooth extraction had on the INR values of patients taking warfarin. One week after tooth extraction, the INR values increased beyond the therapeutic range in 3 out of 110 patients (2.7%). The INR values before tooth extraction in these three patients were close to 3.0. The INR value increased by more than twice as much in 1 of 110 patients (0.9%).

According to the Guidelines for Patients on Antithrombotic Therapy Requiring Dental Extraction 15, tooth extraction can be safely performed without interrupting warfarin when the INR value is below 3.0 [7]. In the present study, when the INR values were below 3.0 in all patients, there were no cases of hemorrhages that required systemic treatment (e.g., vitamin K or clotting factor), or thrombosis (e.g., cerebral embolisms). Post-extraction hemorrhage which required additional treatment such as re-suturing, were observed in seven out of 110 patients (6.4%) (Table 1). In the past, many reports have investigated post-extraction hemorrhages in patients taking anticoagulants, and reported that the incidence of post-extraction hemorrhages was 0–26% [12–16]. Our results were similar to those of other reports [12–16].

Table 1  
Patient data

<b>Variables</b>		
Types of antibiotics	CFPN-PI	57 (51.8)
	AMPC	36 (32.7)
	ABPC + AMPC	9 (8.2)
	AZM	8 (7.3)
Sex	Male	73 (66.4)
	Female	37 (33.6)
Age	Mean $\pm$ SD	72.5 $\pm$ 9.1
	< 75	59 (53.6)
	$\geq$ 75	51 (46.4)
Warfarin dose (mg)	Mean $\pm$ SD	2.72 $\pm$ 1.10
Diabetes mellitus	No	85 (77.3)
	Yes	25 (22.7)
Hypertension	No	57 (51.8)
	Yes	53 (48.2)
Cerebral infarction	No	93 (84.5)
	Yes	17 (15.5)
With antiplatelet therapy	No	82 (74.5)
	Single	27 (24.5)
	Dual	1 (1.0)
Preoperative NSAIDs	No	106 (96.4)
	Yes	4 (0.6)
Serum creatinine (mg/dl)	Mean $\pm$ SD	0.93 $\pm$ 0.30
eGFR (mL/min/1.73 m <sup>2</sup> )	Mean $\pm$ SD	60.0 $\pm$ 16.9
ALT (IU/L)	Mean $\pm$ SD	21.2 $\pm$ 13.8
Number of extracted teeth	Mean $\pm$ SD	2.3 $\pm$ 2.2
	Single tooth	54 (49.1)

Variables		
	Multiple teeth	56 (50.9)
Post-extraction hemorrhage	No	103 (93.6)
(having additional treatment)	Yes	7 (6.4)

It is widely known that an increased age (> 75 years old), high doses of warfarin, renal failure or liver failure, diarrhea, and drug interactions can all cause increases in INR values [17]. Rice et al. conducted a review of many reports and reported that many antibiotics increased INR values, although the duration of administration varied [1]. The mechanism by which antibiotics increase the action of warfarin is known to alter the intestinal flora and decrease the production of vitamin K, thereby enhancing the action of warfarin. Antibiotics also inhibit cytochrome P-450 (CYP) in the liver, increasing the concentration of warfarin in the blood [1]. Several studies have shown that infection and inflammation decrease the expression and activity of CYP, resulting in decreased drug clearance [1, 3]. Other studies have reported that infection itself affects the metabolism of warfarin [3, 4]. In the present study, Case B, whose INR value more than doubled one week after their tooth extraction, was the only one who underwent additional treatments for two post-extraction hemorrhages. Case B might have been the most invasive case, and had evidence of an infection accompanied by necrotic tissue and delayed wound healing one week after tooth extraction.

Several reports have investigated the relationship between various antibiotics and INR values [6, 9, 10, 18]. Ghaswalla et al. reported that there was a significant interaction between time and antibiotics on the INR values of elderly (> 65 years old) patients who were on stable warfarin therapy (AMPC, AZM, levofloxacin [LVFX]) [18]. AZM in particular, which has a significantly long half-life, has been widely discussed in this context [6, 10]. Glasheen et al. reported that INR value increased beyond the therapeutic range in 31% of AZM cases and 33% of levofloxacin LVFX cases one week after oral administration. This was seen in patients on stable warfarin therapy [10]. On the other hand, Kusafuka et al. reported that changes in INR values one week before and after tooth extraction were not statistically significant (2-factor analysis of variance, Not Significant [NS]) when 18 patients taking warfarin were administered AZM [6]. In the present study, changes in INR values throughout the study were not statistically significant (2-factor analysis of variance, NS) for all antibiotics, including AZM. However, in 3 patients whose INR values were close to 3.0 before tooth extraction, the INR values increased beyond the therapeutic range. This result indicates that surgeons have to take attention of medication when the INR value is close to 3.0 before their tooth extraction.

Although most NSAIDs are known to enhance the action of warfarin [5], APAP also requires discussion [19]. Cardeira et al conducted a review of many reports and reported that taking APAP was associated with a mean 0.62 INR increase compared to placebo, for patients taking warfarin [19]. However, in all reports used in this review, the duration of the APAP treatment was longer than four weeks. Because in the present study the APAP treatment was just for 3–7 days after tooth extraction, there may have been

no significant association between APAP and the increase in the INR values one week after extraction. Surgeons need to be wary about prescribing APAP long term.

This study has some limitations. First, there is a possibility of unknown confounding factors and factors not studied (e.g., the presence of diarrhea) due to the retrospective nature of this study. Next, the number of patients was small depending on the antibiotics prescribed. Frequent PT-INR frequent measurements are highly invasive for patients, so we have to make criteria of measurements by patients. In the present study, the INR value increased beyond the therapeutic range in 3 out of 110 patients (2.7%). The INR values were close to 3.0 before tooth extraction in these three patients. Our results suggest that surgeons have to take precautions before performing tooth extraction when INR values are close to 3.0. In addition, in those cases, measuring of INR values one week later may be useful.

## 5. Conclusion

This is the first report to investigate the effects that various antibiotics and analgesics taken for tooth extraction have on the INR values of patients taking warfarin. When tooth extraction is performed in patients taking warfarin, certain factors could increase the INR, such as an interaction between the warfarin and antibiotics or analgesics, post-extraction inflammation or infection, and eating disorders due to post-extraction pain. However, our results suggest that it has little effect on the INR values one week after extraction.

## 6. Abbreviations

prothrombin time-international normalized ratio (PT-INR), surgical site infection (SSI), Infective endocarditis (IE), azithromycin (AZM), cefcapene pivoxil (CFPN-PI), amoxicillin (AMPC), ampicillin (ABPC), acetaminophen (APAP), State of New Jersey (NJ), United States of America (USA), non-steroidal anti-inflammatory drugs (NSAIDs), estimated glomerular filtration rates (eGFR), alanine transaminase (ALT), cytochrome P-450 (CYP), levofloxacin (LVFX), not significant (NS)

## Declarations

### *7.1. Ethics approval and consent to participate*

All patients had oral informed consent regarding tooth extraction, and PT-INR measurements before and after tooth extraction. The PT-INR measurements before and after tooth extraction started more than ten years before by referring to the past reports [1-5]. It has been routinely done since then in our hospital. In this time, we conducted this retrospective observational study to examine the usefulness of the PT-INR measurements and whether it is meaningful to continue from now on. As this study is a retrospective study and planned after total cases finished, patients did not be given informed consent that their PT-INR measurements were for this study, when they had undergone tooth extraction. Instead, exclusion criteria were set for patients who chose not to participate after the publication of this study. This study has been

conducted in full accordance with the World Medical Association Declaration of Helsinki and was approved by the institutional review board of Kakogawa Central City Hospital (authorization number: 2019-84). The ethics committee approved the procedure of this study.

### *7.2. Consent for publication*

Not Applicable

### *7.3. Availability of data and material*

The datasets generated and/or analysed during the current study are not publicly available due [INSERT REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

### *7.4. Competing interests*

The authors declare that they have no competing interest.

### *7.5. Funding*

No funding was obtained for this study.

### *7.6. Authors' contributions*

EI designed the study, performed the data analyses, and drafted the manuscript. AT contributed to study design and data analysis. JK, NT, and TH contributed to data collection and analysis. MA revised the article for important intellectual content. All authors approved the final manuscript.

### *7.7. Acknowledgements*

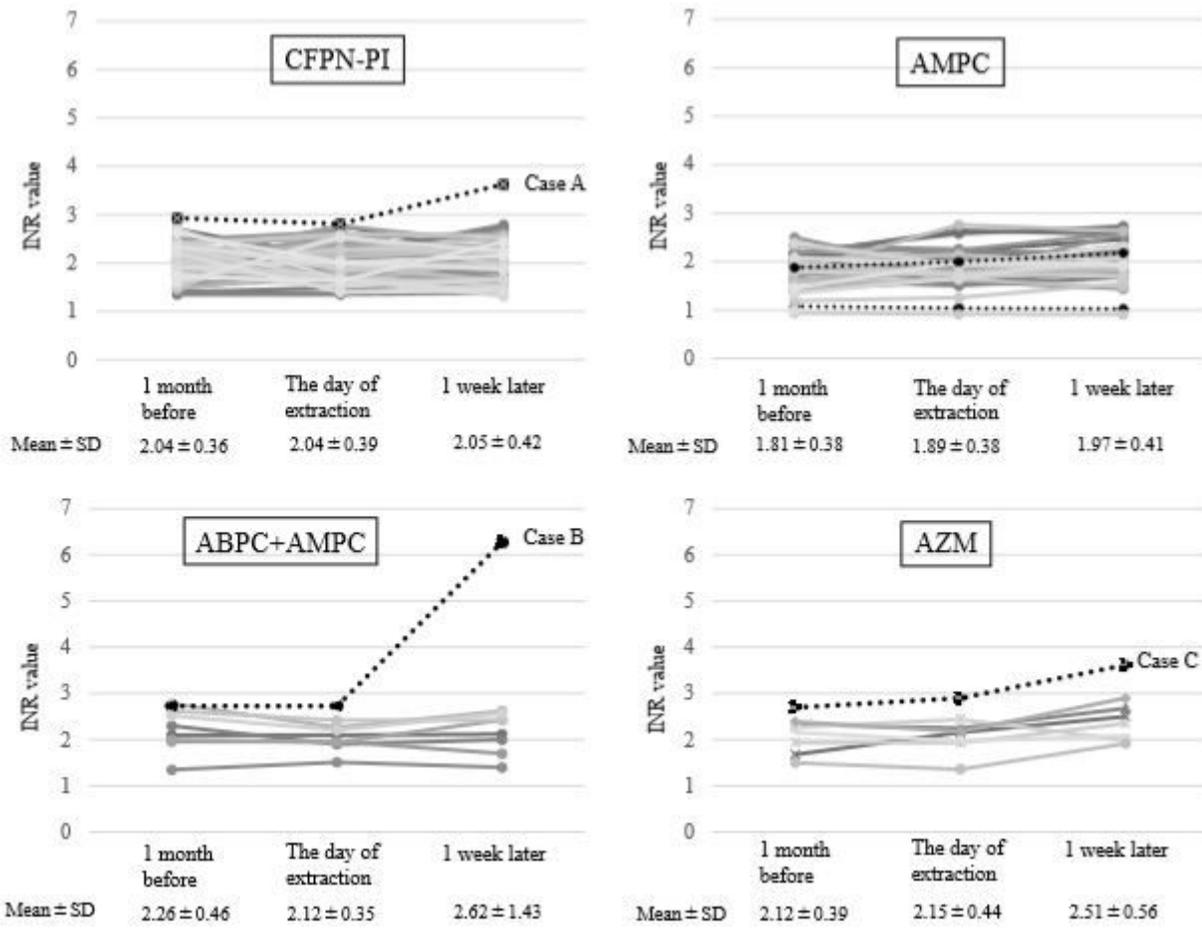
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# Figures



**Figure 1**

Change of INR value with time. The changes in INR throughout the study were not statistically significant. (2-factor analysis of variance, NS)